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I hereby certify that annexed is a true copy of the Provisional Specification as filed on 23 July 2003 with an application for Letters Patent number 527142 made by DOUGLAS PHARMACEUTICALS LIMITED.

Dated 5 August 2004.

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PROVISIONAL SPECIFICATION

A STABLE SUSPENSION FORMULATION

We, **DOUGLAS PHARMACEUTICALS LIMITED,** a New Zealand company, of Central Park Drive, Lincoln, Auckland New Zealand do hereby declare this invention to be described in the following statement:

PT043733136

A STABLE SUSPENSION FORMULATION

Technical Field

The present invention is directed to a stable suspension formulation of clozapine for oral administration and to processes for preparing such formulations.

Background to the Invention

Clozapine (8-chloro-11-(4-methyl-1-piperazinyl-5H-dibenzo[b,e][1,4] diazepine) is a well-known compound having anti-psychotic activity. Details about this compound are disclosed in monograph 2448 of the 13th edition of the Merck Index, the disclosure of which is hereby incorporated by way of reference.

Currently there are no liquid formulations of clozapine commercially available and, as a result, hospital pharmacists are often required to compound liquid formulations using crushed clozapine tablets for patients who have difficulty in swallowing or who feign ingestion.

Clozapine is insoluble in water and therefore the logical option for preparing a liquid formulation is to form it into an aqueous suspension. However, when clozapine is simply added directly to water, the compound settles rapidly to form a dense cake at the base of the aqueous mixture. The caking cannot easily be redistributed and as such would potentially compromise the accuracy of drug dose delivered to a patient.

In order to overcome this, a standard formulation technique would be to use a suitable wetting agent, to promote flocculation. Flocculation is a process where suspended particles agglomerate, forming larger particles that settle loosely and can be readily re-dispersed with gentle shaking thus overcoming the caking problem.

Clozapine is generally regarded as a stable molecule. But, surprisingly, when clozapine is formed into an aqueous suspension with a wetting agent and other formulating agents as might be considered standard in the art, the suspended active was found to be readily susceptible to hydrolysis which was indicated by a marked pH change on extended storage. As a result, the accuracy of the drug dose delivered to the patient could again be compromised.

There would be a clear advantage to be able to provide a physicochemically stable suspension formulation of clozapine for oral administration which would retain its physico-chemical stability over a reasonable storage period. Such a product characteristic would be important to the production of a commercial liquid formulation.

Summary of the Invention

In broad terms the invention in a first aspect may be seen to comprise a physicochemically stable aqueous suspension of clozapine.

In broad terms, the invention in another aspect may be seen to comprise a physicochemically stable aqueous composition including clozapine in suspension together with a wetting agent, wherein the pH of the composition is maintained in the range of about 6 to about 11.

Preferably, the pH is maintained within the desired range using a buffer system.

Preferably the buffer system is a sodium phosphate/sodium hydroxide buffer system.

Preferably the pH is maintained in the range of above about 6 and more preferably from about 6 to about 8.

Preferably the amount of clozapine in the composition is from about 0.1% to about 10% by weight based on the total volume of the composition.

Preferably the wetting agent is present in an amount of between about 0.1% and about 15%

Preferably the wetting agent is selected from a suitable polyalcohol, such as propylene glycol, glycerin, or polyethylene glycol.

Preferably the composition further includes a suspending agent and/or a preservative.

Preferably the suspending agent is present in an amount of between about 0.5% and about 2.0%.

Preferably the preservative is present in an amount of between about 0.0% and about 0.05%.

Preferably the suspending agent is xanthan gum.

Preferably the preservative is methyl paraben and/or butyl paraben.

Preferably the composition further includes a sweetening agent and/or a flavouring substance.

Preferably the composition includes: clozapine, propylene glycol, sodium dihydrogen phosphate dihydrate/NaOH buffer, xanthan gum, methyl paraben, butyl paraben, and water.

Preferably the composition includes about:

(a) 50 mg/mL clozapine;
(b) 40 mg/mL propylene glycol;
(c) 7.8 mg/mL sodium dihydrogen phosphate dihydrate, q.s. sodium hydroxide;
(d) 6.0 mg/mL xanthan gum;
(e) 2.0 mg/mL methyl paraben;
(f) 0.5 mg/mL butyl paraben;
(g) 0.5 mg/mL chlorhexidine gluconate;
(h) q.s. water to final volume.

In a further aspect, the invention may be seen to comprise a method for preparing a physicochemically stable aqueous formulation including clozapine in suspension including the step of controlling the pH of the formulation between about 6 and about 11.

In a further aspect, the invention may be seen to comprise a process for producing a physicochemically stable aqueous composition including clozapine in suspension including the following steps:

(a) stirring the active ingredient clozapine with about three quarters of the propylene glycol ascribed to the batch;

(b) addition of the buffer salt (and optionally sweetening agents) dissolved in about half the volume of water ascribed to the batch with constant stirring;

(c) adjusting the pH value with the base component of the buffer with mixing;

(d) addition of the preservatives dissolved in the remaining propylene glycol;

(e) slow addition of the suspending agent with continuous stirring until the mixture thickens;

(f) further diluting the suspension with water to the desired end-volume.

Detailed Description

The present invention is broadly concerned with the preparation of a physicochemically stable suspension formulation of clozapine for oral administration.

Clozapine is generally regarded as a stable molecule which is practically insoluble in water. On addition of clozapine directly to water, the drug settles to form a dense cake at the base of the mixture which cannot be readily redistributed. When a wetting agent was used, the caking problem was overcome but it was surprisingly found that the active was readily susceptible to hydrolysis. As a result, the clozapine suspension was not suitable for commercial use as it could not be stored for a reasonable period to allow later, accurate, use.

Unexpectedly, it has been found that it is possible to impart considerable stability to an aqueous suspension of clozapine if the pH of the aqueous suspension is controlled and maintained at a level between about 6 and about 11. Preferably the pH will be maintained within the range of 6 to 9 and more preferably between 7 and 8. If the pH is not controlled and maintained within this range, the active degrades quite quickly.

In order to control the pH, a suitable buffer system should be used. Buffer systems comprise mixtures of appropriate amounts of conjugate bases of various organic acids adjusted to the desired pH value with NaOH or HCl. Examples of suitable bases include but are not limited to: sodium citrate, potassium citrate, sodium bicarbonate, potassium bicarbonate, sodium dihydrogen phosphate and potassium dihydrogen phosphate. The buffer should have sufficient capacity to remain in the desired pH range throughout the product shelf life. Such issues would be well known to the skilled person.

The preferred buffer system is sodium dihydrogen phosphate/sodium hydroxide where the phosphate concentration ranges from about 10 mM to about 50 mM. Below about 10 mM there is insufficient capacity to control the pH on prolonged storage, while phosphate concentrations above about 50 mM have been found to promote recrystallisation of the drug substance.

The amount (w/v) of clozapine in the composition will be a suitable amount as will be known to the skilled person in the art. Ranges between 0.1% to 10%, preferably from 2.5% to 7.5% in particular 5% (50 mg/mL) would be used. As will be known to the skilled person, simple dilution of the suspension could be used to deliver a required dosage amount to a patient as needed.

The wetting agent used in the composition is preferably selected form any one or more of propylene glycol, glycerin or polyethylene glycol and like compounds as would be known to the skilled person. The % range of wetting agent in the composition will preferably be between about 0.1% and 15% , more preferably between 1% and 10%.

An alternative formulation could use higher levels of polyols such as propylene glycol or glycerin as these would limit degradation of clozapine in prolonged storage. Polyols such as the PEG's would still allow clozapine to the readily solubilised and degradation would follow. Levels of up to 60% w/v could be used. Higher levels (95% w/v glycerin, 5% clozapine, 0.05% w/v chlorhexadrin gluconate) may also be possible. As discussed herein, water is, however, the preferred suspension vehicle with polyol inclusion limited to wetting agent levels.

The oral suspension according to the present invention will preferably also include a preservative to prevent the growth of micro-organisms such as bacteria, yeasts and fungi. The preservative should also be physicochemically stable in the pH range of 6 to 9. Suitable preservatives include could be selected from any one or more of: chlorhexidine ; methyl paraben; propyl paraben; butyl paraben and their salts; diazolidinyl urea (Germall II.RTM); quaternary compounds, eg benzalkonium chloride and cetylpyridinium chloride e, phenyl ethyl alcohol and the like. The concentration of preservatives may range from about 0.01% to about 0.5%.

When preparing a formulation with the active suspended in an aqueous carrier it is often necessary to add a stabilizing agent or agents to prevent settling of the active material.

Over time the settling (even if ordinarily capable of redistribution) could lead to caking of the active to the inside walls of the product pack, leading to difficulties with redispersion and accurate dispensing. Suitable stabilising agents include but are not limited to xanthan and tragacanth gums, Avicel RC-591 (microcrystalline cellulose/ sodium carboxymethyl cellulose), polyvinyl pyrolidone, Carbopol.RTM (carboxyvinyl polymer).

A variety of sweeteners and flavourings could also be added as desired and as known to the skilled person. Additives such as sucrose and/or banana flavouring, for example, could be added.

Compositions according to the present invention have been characterised by their improved physicochemical stability. The term "physicochemically stable", or similar terms, refer to an aqueous suspension formulation wherein, after storage for a period of up to about three months at a temperature of 40°C, the residual amount of clozapine is 95% or more of the initial clozapine concentration.

The term clozapine as used herein, refers to the free base form and pharmaceutically acceptable acid addition salts thereof. Possible salts include, but are not limited to, inorganic salts such as phosphates, carbonates and organic salts such as citrate and acetate. The term addition salt also includes the solvates of clozapine including, but not limited to, hydrates and alcoholates.

The aqueous suspensions according to the present invention are well suited to dilution with acidic non-alcoholic beverages such as citrus drinks, soft-drinks and the like. This option aids the palatability of the liquid and may result in improved patient compliance. As stated earlier, the dilution requirements to achieve an effective clozapine dosage would be well within the knowledge of the skilled person in this particular art.

A particular oral composition according to the present invention comprises:

(a) clozapine;
(b) a suitable wetting agent to disperse the drug substance;
(c) a suitable buffer to control the pH in the range of 6 to 9;
(d) a stabilizing agent;
(e) a preservative; and
(f) water

Preferably the clozapine would be present in an amount of between about 0.1% and 10%; the stabilising agent between about 0.5% and 2%; and the preservative between about 0.01% and 0.05%.

A more preferred oral composition according to the present invention comprises:

(a) 5.0% (50 mg/mL) clozapine;
(b) 4.0% (40mg/mL) propylene glycol
(c) 0.78% (7.8 mg/mL) sodium dihydrogen phosphate dihydrate and sufficient sodium hydroxide to adjust the pH range from 6 to 9;
(d) 8.0% (80 mg/mL) sucrose;
(e) 0.60% (6.0 mg/mL) xanthan gum;
(f) 0.2% (2.0 mg/mL) methyl paraben;
(g) 0.05% (0.5 mg/mL) butyl paraben;
(h) 0.05% (0.5 mg/mL) chlorhexidine gluconate
(i) water q.s to 100% (approx. 81.3 mg/mL).

The NaOH concentration used for adjustment of pH is preferably 4.6 M.

In particular, the process may comprise the following steps:

(a) stirring the active ingredient clozapine with about three quarters of the propylene glycol ascribed to the batch;
(b) addition of the buffer salt (and optionally sweetening agents) dissolved in about half the volume of water ascribed to the batch with constant stirring;
(c) adjusting the pH value with the base component of the buffer with mixing;
(d) addition of the preservatives dissolved in the remaining propylene glycol;
(f) slow addition of the suspending agent with continuous stirring until the mixture thickens;
(g) further diluting the suspension with water to the desired end-volume.

EXAMPLES

The following examples are intended to illustrate the scope of the present invention in all its aspects but not to limit it thereto.

Example 1

F1: Oral Suspension (pH =7.0)

Ingredient	Quantity (mg/mL)
Clozapine	50
Propylene Glycol (I)	30
Sodium Dihydrogen Phosphate Dihydrate	7.8
Sodium hydroxide	q.s ad pH =7.0
Sucrose	80
Xanthan Gum	6.0
Propylene Glycol (II)	10
Methyl Paraben	2.0
Butyl Paraben	0.5
Chlorhexidine Gluconate	0.5
Water	q.s ad 1mL

(1) Clozapine (50 mg) was mixed into a paste with Propylene Glycol (30 mg).

(2) Sodium Dihydrogen Phosphate Dihydrate (7.8 mg as a 1 M solution) was added to Fraction (1) with stirring.

(3) Sucrose (80 mg), dissolved in 0.35 mL of water was added to Fraction (2) with stirring.

(4) NaOH (4.6 mol/L) was added to Fraction (3) to adjust the pH to about 7.0.

(5) Methyl Paraben (2 mg)and Butyl Paraben (0.5 mg) were dissolved in Propylene Glycol (10 mg) with gentle warming.

(6) Fraction (5) was added slowly to Fraction (4) with constant stirring.

(7) Chlorhexidine Gluconate (0.5 mg) was dissolved in 0.2 mL of water.

(8) Fraction (7) was added to Fraction (6) with constant stirring.

(9) Xanthan Gum (4.8 mg) was slowly added to Fraction (8) with constant stirring taking care not to aerate the suspension.

(10) Fraction (9) was further diluted with water to 1 mL.

In a similar way there were prepared:

F2: Oral Suspension (pH = 6.0 ± 0.1)

Ingredient	Quantity (mg/mL)
Clozapine	50
Potassium Dihydrogen Phosphate Dihydrate	4.7
NaOH	q.s. ad pH =6.0
Sucrose	80
Xanthan Gum	5.0
Potassium Sorbate	2.0
Water	q.s. ad 1 mL

F3: Oral Suspension (pH = 7.0 ± 0.1)

Ingredient	Quantity (mg/mL)
Clozapine	50
Potassium Dihydrogen Phosphate Dihydrate	4.7
NaOH	q.s.ad pH = 7.0
Sucrose	80
Xanthan Gum	5.0
Potassium Sorbate	2.0
Water	q.s. ad 1 mL

F4: Oral Suspension (pH =8.0 ± 0.1)

Ingredient	Quantity (mg/mL)
Clozapine	50
Potassium Dihydrogen Phosphate Dihydrate	4.7
NaOH	q.s. ad pH = 8.0
Sucrose	80
Xanthan Gum	5.0
Potassium Sorbate	2.0
Water	q.s. ad 1 mL

Example 2

The table herein below summarizes the clozapine concentrations measured after a particular storage time of the composition at a particular temperature, expressed as the percentage of the initial clozapine concentration.

Formulation	F1	F2	F3	F4
1 month @5°C	102.3	102.6	101.0	100.2
1 month @ 50°C	98.4	100.6	101.1	102.7
3 month @ 40°C	omitted	104.7	omitted	97.8

Administration of the Suspension

It is envisaged that the product would be supplied in a glass or plastic container with a child proof closure together with a syringe marked in mL for ease of dosing. The minimum marked volume of the syringe would be 0.25 mL to allow for accurate dosing of the recommended starting dose of 12.5 mg based on the Clozapine 50 mg/mL product. The maximum volume of the syringe would be around 10 mL to allow ready dispensing of the range of most therapeutic doses in one application. The syringe should be emptied into a non-alcoholic drink with stirring. Orange juice, coffee and some carbonated soft drinks are suitable. The syringe should be rinsed and dried after use.

The foregoing describes the invention including preferred forms thereof, alterations or modifications as would be obvious to a person skilled in this particular art are intended to be included within the scope of the invention as described.

DOUGLAS PHARMACEUTICALS LIMITED

By Their Attorneys

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